Three Common Genetic Variants Predict Type 2 Diabetes

Prospective studies of genetic risk for disease are difficult to conduct but can yield unique information on the risk of developing a chronic disease. A group from Sweden undertook a very ambitious project: to prospectively follow over 7,000 adults in order to explore genetic predictors of the development of type 2 diabetes. Valeriya Lyssenko, MD, PhD of Lund University in Sweden presented data from this group of patients who have been followed for 22 years. Patients were a randomly selected subgroup drawn from those participating in the Malmo Prevention Project, a large randomized controlled trial aiming to decrease deaths related to cardiovascular disease, breast cancer, and alcohol abuse. Patients did not have diabetes at baseline and were followed from 1974-1992 with an additional follow up visit in 2002. DNA obtained from the subjects was analyzed for genetic variants. The nine genes that were studied were PPARG, KCNJ11, CAPN10, UCP2, IRS1, PGC1A, PTPN1, ENPP1, and TCF7L2.

At the follow up visit in 2002, 1,422 (20.1%) of the participants had developed type 2 diabetes. The researchers focused their efforts on these patients to see which genes may have predicted onset of the disease. Three genetic variants were identified that appeared to confer additional risk for developing type 2 diabetes: 2 different polymorphisms of the TCF7L2 gene (odds ratio 1.40 and 1.52), a KCNJ11 variant (odds ratio 1.23), and a PPARG variant (odds ratio 1.20). A person having all three variants had the highest risk of developing diabetes (odds ratio 2.79; $p<0.0001$). In this study, certain TCF7L2 variants appeared to influence glucose and insulin responses during oral glucose tolerance tests (OGTT; $p<0.05$ compared to normal controls), indicating that this variant is associated with impaired beta cell secretion. People with the KCNJ11 variant were also found to have impaired insulin secretion during OGGT ($p=0.014$) and intravenous glucose tolerance tests ($p=0.025$). Additional analyses suggest that the PPARG variant was associated with enhanced insulin sensitivity and protection against diabetes in lean individuals ($p=0.004$ vs. obese individuals).

So what does this mean for the prevention of diabetes? “While theoretically someone could now be tested to find out whether they have these risk-producing genes, that won’t tell you for sure whether you will get diabetes because there are other genes that have yet to be identified — and genes must interact with environmental factors in order for the predisposition to be triggered and the disease to unfold,” said Dr. Lyssenko. It is her hope that eventually a genetic screening test could be developed to identify people at risk so that interventions could prevent disease onset.

For more exciting news about the TCF7L2 variant, visit www.nejm.org.